Fragrance Safety & Evaluation

AA WORKSHOP - SACRAMENTO
SEPTEMBER 15, 2011

Kevin J. Renskers, Ph.D.
Chairman IFRA Scientific Committee

- Research Institute for Fragrance Materials
- Vision: To be the international scientific authority for the safe use of fragrance materials
- Non-profit organization funded by Industry (raw material suppliers, fragrance manufacturers, consumer product companies)
- Key is the RIFM Expert Panel (REXPAN)

- International Fragrance Association
- Trade association for the global fragrance industry
- Membership consists of direct member companies and national trade associations
  (e.g., IFRA-North America)
- Members represent > 95% by volume of all fragrances manufactured globally
- Primary mission is to ensure the safety of fragrance materials through a dedicated science program

Fragrance Industry Safety Program

Working together …

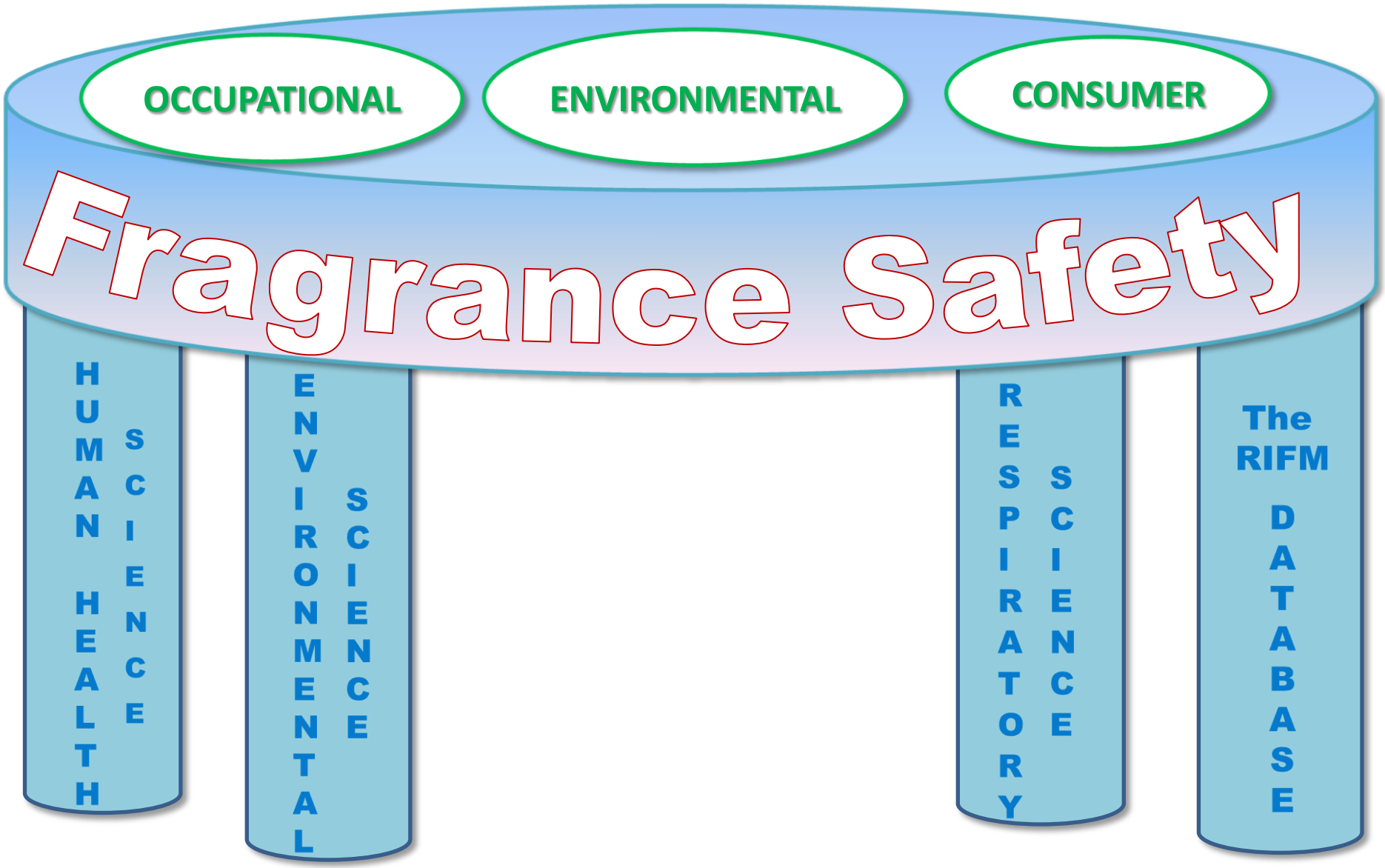
RIFM™

- Human Health
- Respiratory
- Environmental
- Database
- REXPAN
- REACH

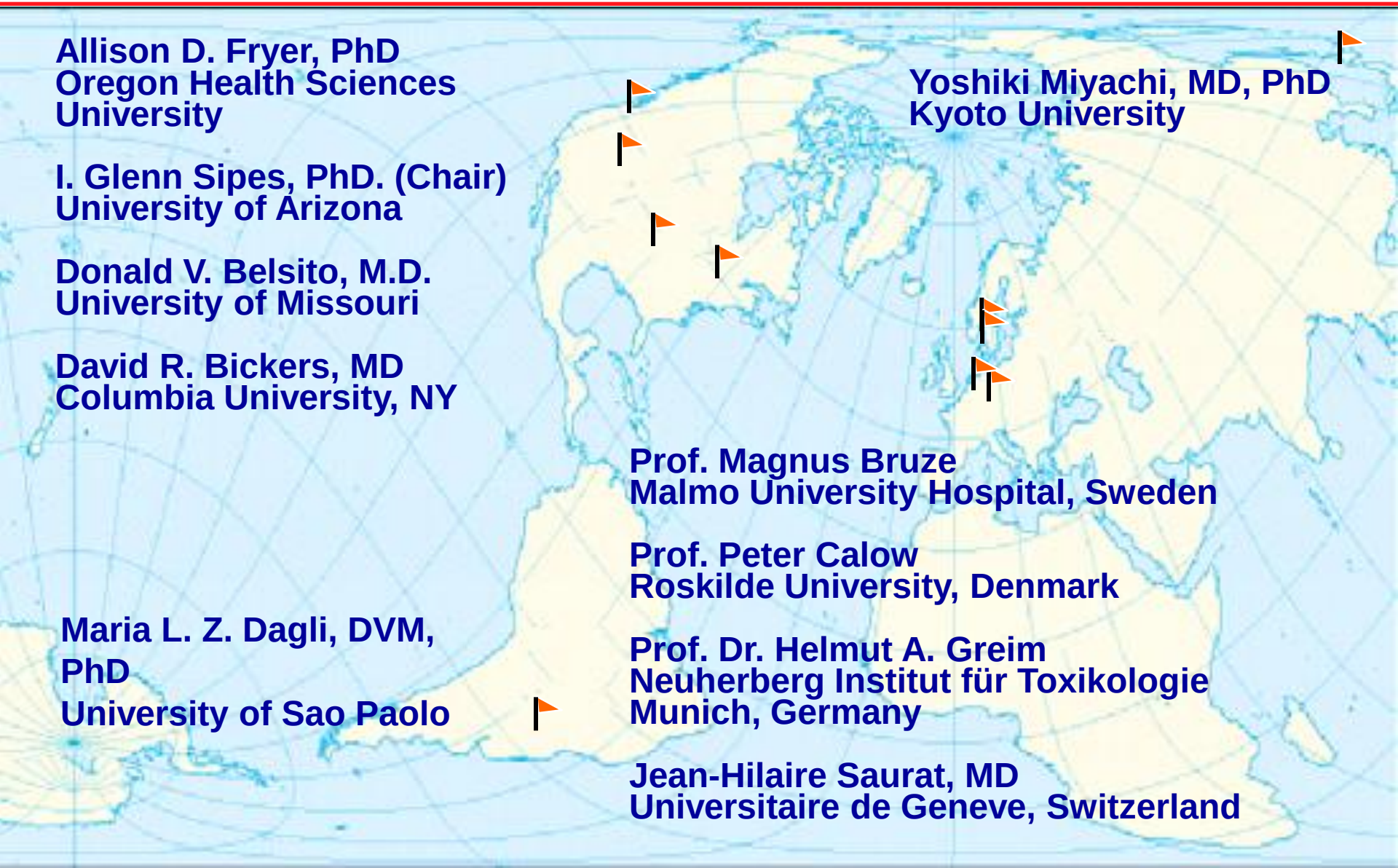
ifra
INTERNATIONAL FRAGRANCE ASSOCIATION

- Code of Practice
- Standards
- Compliance
- Committees
- Communications
- Advocacy

The Platform



RIFM Expert Panel



Allison D. Fryer, PhD
Oregon Health Sciences University

I. Glenn Sipes, PhD. (Chair)
University of Arizona

Donald V. Belsito, M.D.
University of Missouri

David R. Bickers, MD
Columbia University, NY

Yoshiki Miyachi, MD, PhD
Kyoto University

Prof. Magnus Bruze
Malmo University Hospital, Sweden

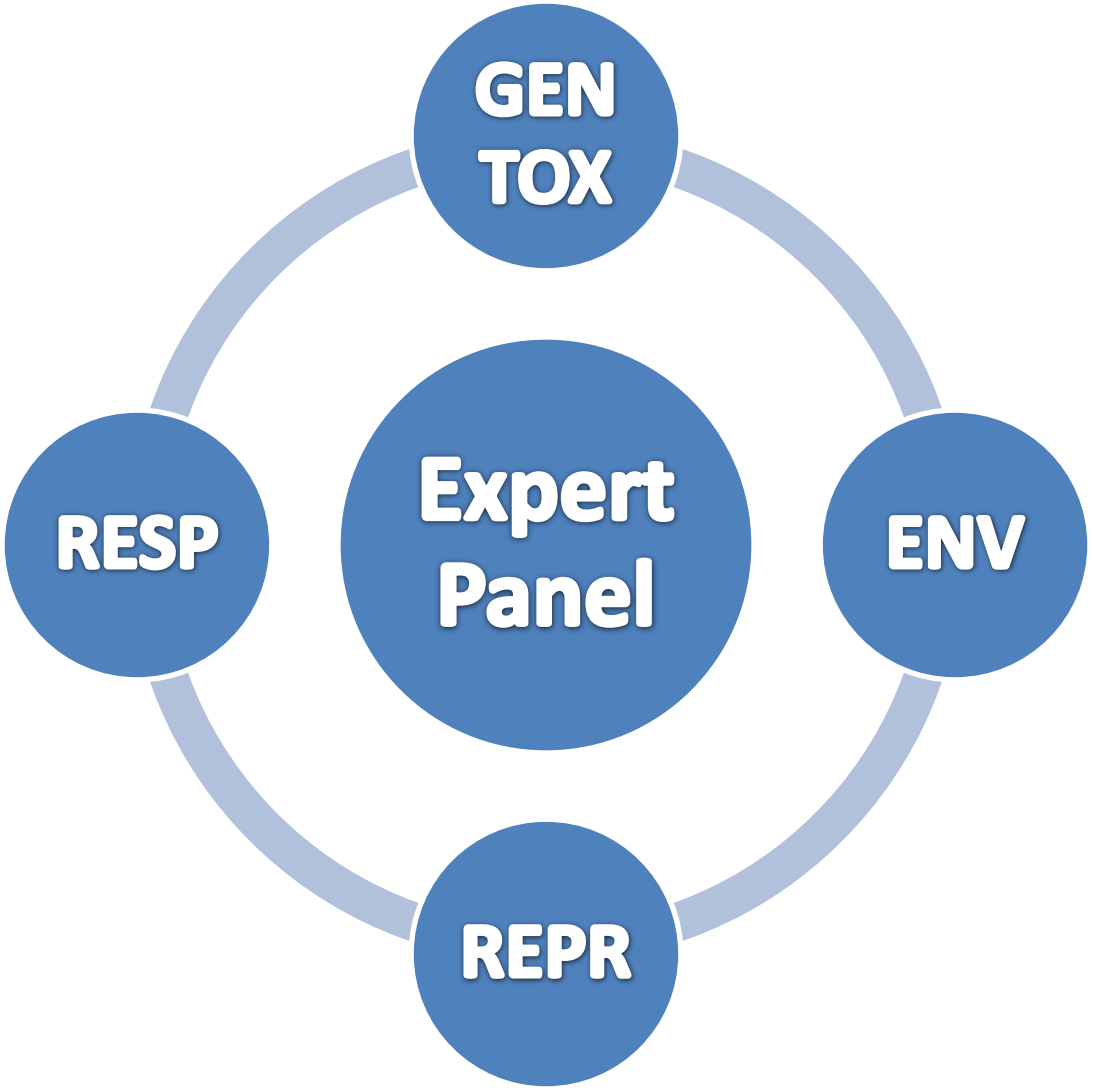
Prof. Peter Calow
Roskilde University, Denmark

Prof. Dr. Helmut A. Greim
Neuherberg Institut für Toxikologie
Munich, Germany

Jean-Hilaire Saurat, MD
Universitaire de Geneve, Switzerland

Maria L. Z. Dagli, DVM, PhD
University of Sao Paolo

Expert Panel Adjuncts



Fragrance Safety Review Can Result in IFRA Standards

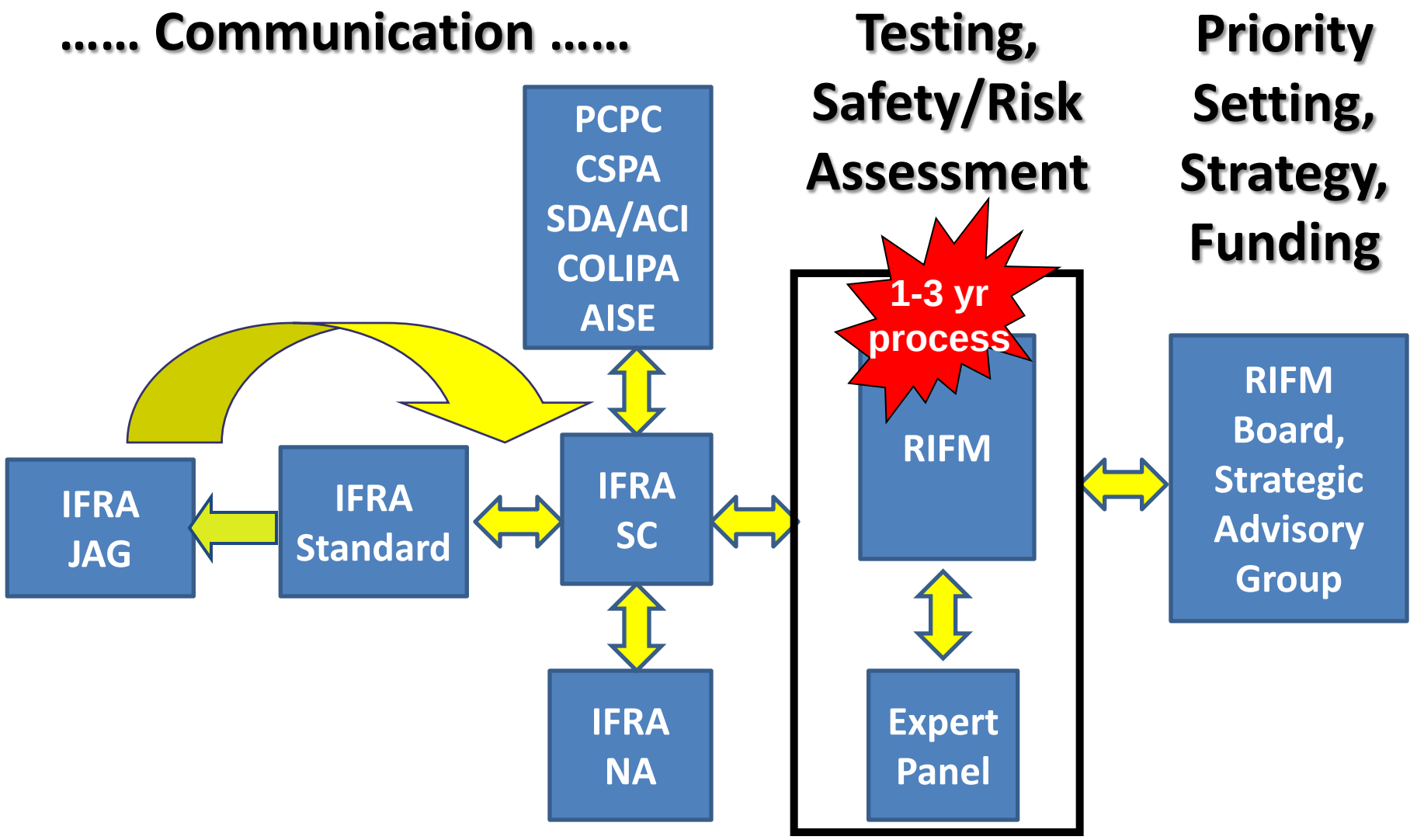
DOSSIER	→	RIFM, IFRA SC
EVALUATION	→	REXPAN
STANDARD	→	IFRA SC
CONSULTATION	→	ASSOCIATIONS CLIENT INDUSTRY
FINAL WORDING	→	REXPAN
COMMUNICATION	→	IFRA SECRETARIAT

Fragrance Industry Self-Policing

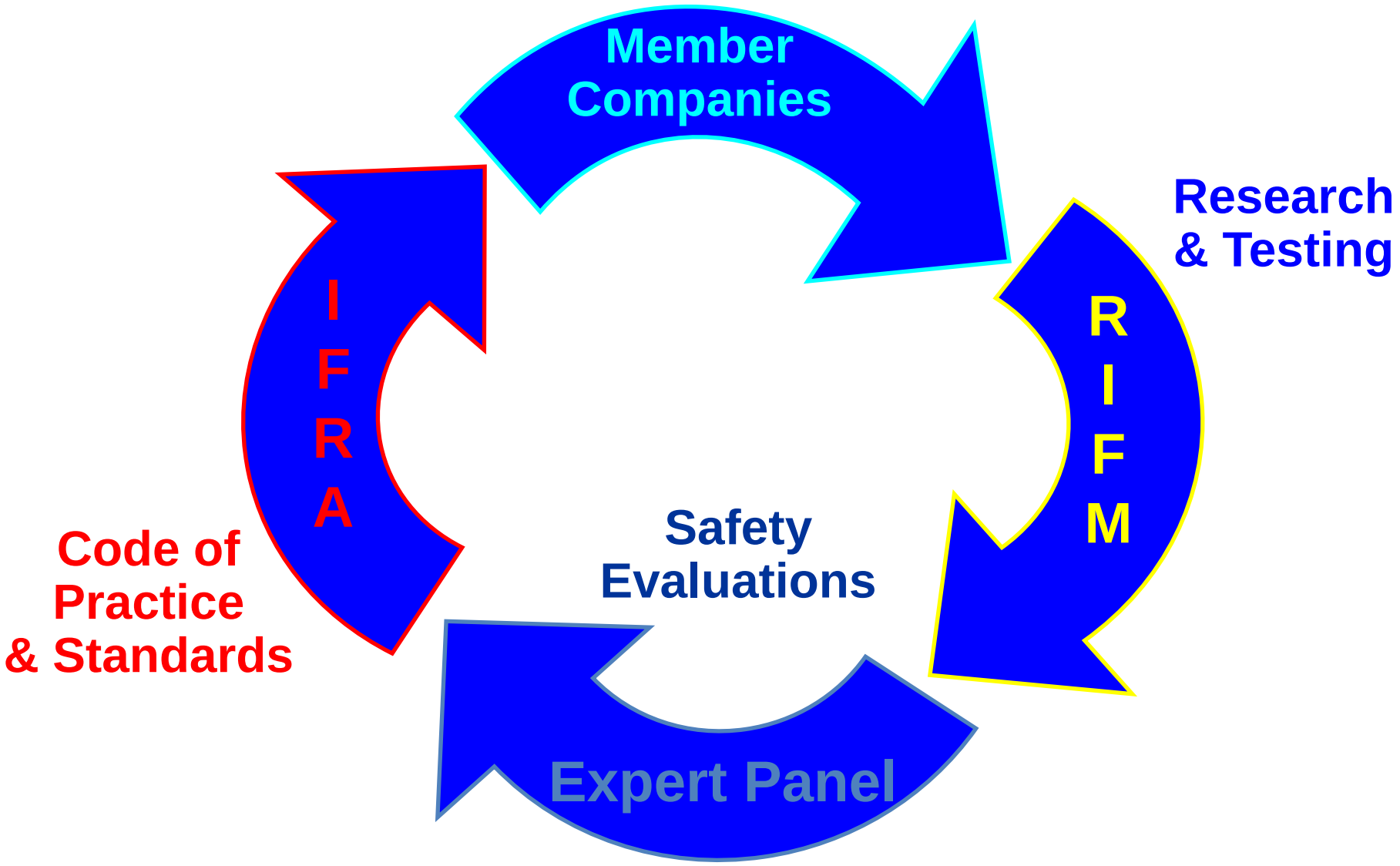
- IFRA Code of Practice
  - National Association bylaws require adherence
  - GMP and use guidelines, definitions, labeling claims
  - Intellectual property
- IFRA Standards
  - > 200 = specifications, prohibitions, restrictions
- IFRA Compliance Program
  - Verification through 3rd party analysis
  - Protocols for collection of consumer products, sample preparation, communication of violation, corrective action, confidential information
  - Four years of no prohibited materials found

Science Issue & Communication

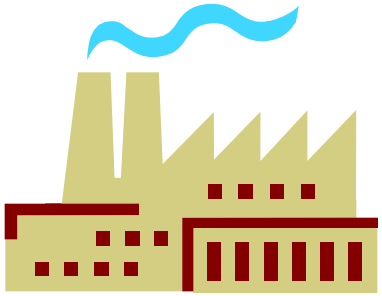
Priority Setting and Management



Fragrance Product Safety



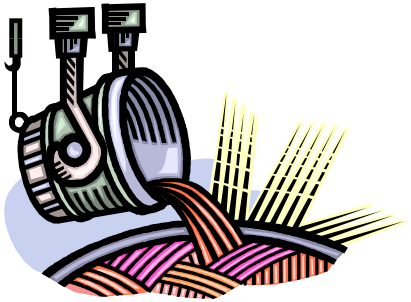
Safety Information Flow



Manufacturer

RIFM

Consumer Company



Fragrance Supplier

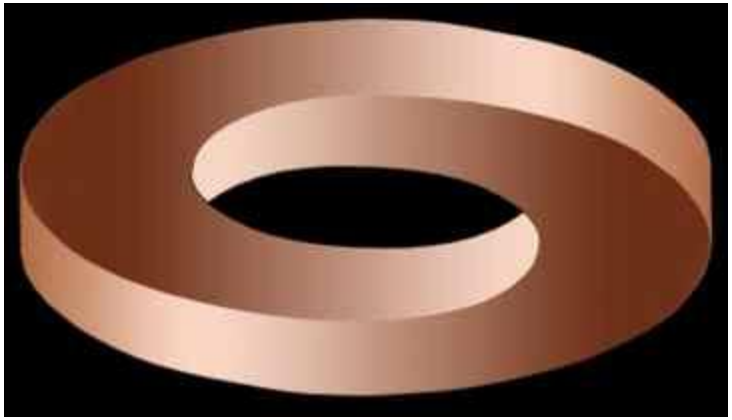
Transparency

- REXPAN safety reviews of fragrance material groups published in peer-reviewed scientific journals
- IFRA Ingredient List, posted on the IFRA public website, is a complete list of all fragrance materials used by the IFRA membership

Substitutes Must Be Safe!

"Yes, but it's naturally toxic."

Thank You!



Alternative Assessment in Personal Care: A Case Study

Alternative Analysis III – Symposium
Thursday, September 15, 2011
Byron Sher Auditorium, Cal/EPA Building

Personal Care Products Council
Committed to Safety, Quality & Innovation

Collaborators:

- Jack Linard, Unilever (Presenter)
- Jay Goldring, L'Oreal
- Carl D'Ruiz, Dial-Henkel
- Maryann McKeever, Esteé Lauder
- Scott Belanger, Procter & Gamble
- Tom Myers, Personal Care Products Council
- John Krowka, Personal Care Products Council

Identifying Potential Chemical Issues

- **Trained staff continuously review study results and monitor current and new information on cosmetic ingredients**
  - Literature
  - Consumer complaints/opinions
  - Press
  - Internal consumer or safety studies
- **Human Safety Assessments also conducted under CIR, industry-sponsored safety evaluation program**
  - Cosmetic Ingredient Review (CIR) Mission: To thoroughly review and assess the safety of ingredients used in cosmetics in an open, unbiased, and expert manner, and publish the results in the peer-reviewed scientific literature
  - CIR meetings are open to the public
  - Seven CIR Expert Panel voting members, publicly nominated by consumer, scientific, and medical groups, government agencies, and industry
  - Expert Panel members must meet the same conflict of interest requirements as individuals serving on FDA advisory committees
  - Three liaison members, which serve as nonvoting members, include representatives from FDA, the Consumer Federation of America, and PCPC

Identifying Potential Chemical Issues (continued)

Regulatory Compliance

Personal care products and ingredients are assessed to ensure compliance with regulatory requirements:

Federal:

- FDA
- OSHA
- EPA
- DOT
- Other (FTC, CPSC)

State:

- Myriad (and differing) state requirements

International:

- EChA (R.E.A.C.H.)
- EU Cosmetics Regulation
- Canada (CEPA, Canadian Cosmetics Regulation)

Examples of Information Reviewed for Safety Assessments

- **Exposure analysis (Human and Environmental)**
  - Possible routes of exposure
  - Quantitative exposure estimates
- **Chemical structure information**
  - Structural alert identification
  - Information on chemical class
- **Human health study results**
  - Genotoxicity
  - Dermal irritation/sensitization
  - Reproductive hazards
  - Ocular irritation
- **Environmental study results**
  - Biodegradability
  - Ecotoxicity

Scientific Safety Assessment

- **Does a potential hazard exist?**
  - Study quality
  - Complaint analysis (types, frequency)
  - Statistical analysis
  - Scientific plausibility
- **Risk Assessment**
  - If potential hazard exists, is risk in the formulated product meaningful?
  - Relevance of exposure
    - Biodegradability/ecotoxicity results for leave-on products
    - Results of oral testing for topical products
    - Extent of absorption
  - What are benefits of substitution?
- **Timing for substitution**
  - Immediate
  - Long-term

Case Study: *Geranyl Nitrile (GN)*

- **Common fragrance ingredient**
- **Longstanding history of safe use**
- **Required testing (OSHA, EChA) revealed genotoxicity**
  - No significant human health hazard identified; nevertheless, removal of GN over time was deemed appropriate to eliminate any potential hazard
- **"Prohibited" under IFRA standards in 2006**
  - No government prohibitions to date

Case Study: *Geranyl Nitrile (continued)*

- **IFRA members voluntarily began reformulating out of GN in 2006-2007**
  - Thousands of products reformulated or discontinued
  - Rigorous Health Hazard & Risk Assessment by Experts determined that there was no significant human health hazard for products with it
  - Removal of the ingredient was done quickly to meet IFRA timetable but still took 1+ years to complete
- **Environmental Assessment: determined as environmentally safe**
  - Assessed by conventional risk assessment methodologies known to and used by industry and the USEPA
  - GN is not acutely toxic to representative aquatic organisms
  - Volumes discharged into the aquatic environment are quite low, thereby limiting exposure to aquatic life

Generic Outline of Process to Substitute One Fragrance

Step 1: **Identify formulations with a fragrance containing that ingredient**

- Fragrance Supplier provides information to customers

Step 2: **Determine when proposed substitutes will be available**

- Approximately 1-3 months while fragrance house develops, evaluates, tests alternatives
- Identify whether alternative ingredient needs to be reported under California Safe Cosmetics Act of 2005

Generic Outline of Process to Substitute One Fragrance (continued)

Step 3: **Prepare and evaluate products with substitute**

i. **Initial Laboratory and Pilot Plant work commences**

ii. **Stability Work commences**

a. Typically 3 months minimum @ high temperatures
b. Room Temperature Controls for up to 3 years
c. Consumer Tests
d. Safety Assessment of new formulation
e. Small Scale Gross Negative Tests
f. Extensive Testing for Products in which Fragrance is critical selling point

iii. **Advertising Claims and Regulatory Support**

a. Ensure previous claims are still valid

- Additional product testing and evaluation may be needed

iv. **Failure? = Back to Beginning**

Generic Outline of Process to Substitute One Fragrance (continued)

Step 4: Manufacture

i. Scale-up production trials
   - Comparison with standards

ii. Full Manufacture
   - Up to 3 Months before product gets into stores

Step 5: Post-Launch Activity

i. Monitor Consumer Hot-Lines & Adverse Events (as normal)

Immediate Impact on Industry

- **The substitution of just one chemical, Geranyl Nitrile, significantly impacted personal care products companies, affecting *thousands* of fragrances and at least as many products**
  - In some cases GN could be replaced by a straight substitution with another single ingredient
  - More commonly, such ingredient removal necessitates a complex substitution program which requires reformulation and rebalancing of the product to match the original performance (odor, stability, efficacy)

Product Reformulation with Modified Fragrances: P&G Experience

- **For P&G, approximately 800 perfume formulations were impacted by the Geranyl Nitrile re-formulation**
  - Involved the cooperation of 5 R&D sites on 3 continents, 3 manufacturing sites where formulations are produced, and numerous supplier sites
  - P&G estimated 2 FTEs for 1.5 years simply to manage the information for GN (e.g, approval of new formula cards, entry into regulatory and product development database, development of new disclosures for future reformulations, etc.)
    - This does not include Perfume R&D, Product Development R&D, or Purchasing, which involved significant effort as well
  - Estimated Cost for One Ingredient Change: approximately **$4.5 million**

Product Reformulation with Modified Fragrances: P&G Experience (continued)

- **Perfume Raw Material (PRM)**
  - Cost associated with identification of substitute PRM(s) – identifying appropriate replacement material(s)
  - Increased costs associated with new PRM(s)
- **Fragrance Formulation**
  - Cost of qualification of the new PRM(s) in the fragrance formulation
  - Cost of qualification of the new fragrance formulation
- **Product Formulation**
  - Cost of qualification of the new fragrance in the product formulation
  - Reformulation of products as a result of qualification studies
- **Ancillary Product Issues**
  - Cost of product labels/ingredient statement modifications/re-registration of products
  - Scrapping of perfumes

Benefits of Regulatory Flexibility

- **Flexible regulations would provide greater benefit to California consumers than prescriptive mandates.**
  - **Cost to State of California to regulate industry**
  - **Self-regulation leaves the obligation, and thus the liability, of safety with the manufacturers**
  - **Industry is motivated and committed to product safety and is in the best position to assess the safety of its products**
  - **Government mandates mean industry "waits" for the regulators to enforce changes**

Conclusions

Industry is Committed to Safety

- Industry is committed to ensuring that all products are safe for use by consumers and comply with appropriate regulations
  - FDA requires cosmetic manufacturers to assess safety of product formulations
- Personal care industry has a long and successful history of identifying and evaluating chemicals of concern
  - Continuous monitoring and evaluation using state of the art test protocols
  - Scientific analysis
  - Timely action
  - Above and beyond significant global regulatory requirements
- Safety assessments, which evaluate hazards of specific chemicals and their exposure to relevant populations , are periodically reviewed as new data become available
- Industry takes proactive initiatives when warranted, without waiting for regulations to catch up

Conclusions

Need for Flexibility in Regulations

- Must allow flexibility to keep up with current developments
- Prescriptive requirements will hamper innovation

Substitution Will Have Major Repercussions

- Performing Alternatives Assessments and making any resulting changes is a complex operation and is done by manufacturers of products on a global basis
- Substitution process may be costly and time-consuming
  - Want to ensure product quality is not affected
  - Scientific analysis crucial to determining course of action